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Black Water Fever in Severe Falciparum Malaria: A Case Report

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Abstract

Introduction: Black water fever (BWF) is a complication of severe *Plasmodium falciparum* infection in hemolysis of erythrocytes into the bloodstream releasing the hemoglobin directly into the blood vessels and causes severe anemia and passage of dark/cola color urine, leading to acute renal failure. Hemoglobinuria or BWF is a rare and severe manifestation of falciparum malaria characterized by sudden intravascular hemolysis followed by fever and presence of abnormal hemoglobin in the urine. **Aim:** The aim of this study was to diagnose and treat severe malaria infection in a Nigerian patient admitted to the Casualty of the IDH Hospital. **Case Presentation:** A 20-year-old Nigerian boy came to Kuwait and started complaining abdominal pain, nausea, vomiting and fever two days after his arrival. The investigation revealed high fever (40.8˚C), heart rate 125, blood pressure of 100/60 mmHg. The physical examination was unremarkable, including a normal neurologic examination, no hepatosplenomegaly, rash and neck rigidity. The Giemsa stained thick and thin blood examination confirmed the severe infection of *Plasmodium falciparum* with 41.0% parasitemia. The patient was admitted to the hospital and started intravenous Quinine (1200 mg loading dose in 5% glucose over 4 hours). The patient was feeling much better on next morning but became unconscious by evening and shifted to ICU. His all CBC parameters were higher and started passing dark/cola color urine. The 12 units of whole blood were exchanged on next morning and became fully conscious on 4th day and his anemia and thrombocytopenia were improved and the color of the urine also became normal. **Conclusion:** Quinine is used in both complicated and uncomplicated malaria and may cause black water fever in severe infection of *P. falciparum*. It is caused by the hemolysis of erythrocytes due to malaria and also with the metabolism of quinine, making these cells more

vulnerable to hemolysis in falciparum malaria and also in G6PD deficiency.

Keywords

Black Water Fever, Hemoglobinuria, Malaria, Quinine, Chloroquine

1. Background

Black water fever, also called malarial hemoglobinuria, is one of the less common yet most dangerous complications of malaria. The term black water fever (BWF) has been taken from the French word "fièvre bilieuse mélanurique" [1], generally used for a febrile syndrome with intermittent passage of dark-red to black colored urine in falciparum malaria at very high parasitaemia on peripheral blood smear and the symptoms of renal failure, circulatory compromise, pallor, jaundice, nausea, vomiting, and epigastric pain [2] [3].

BWF is mostly associated with *Plasmodium falciparum* infection [4], but cases have also been documented in *Plasmodium vivax* [5] or in a mixed infection of *P. falciparum* and *P. vivax*, *Plasmodium malariae* [3], and *Plasmodium knowlesi* infections [6] [7]. In the beginning of twentieth century, the number of BWF cases was very high due to the use of Quinine as a treatment of malaria. There was a dramatic decrease in the incidence of BWF when chloroquine superseded quinine in 1950 and the reemergence of BWF following the reintroduction of quinine due to chloroquine resistance and introduction of mefloquine and halofantrine both strongly suggested that amino-alcohol drugs play a role in the etiology of BWF [8] [9] [10] [11] [12]. The massive hemolysis of red blood cells occurs in severe *Plasmodium falciparum* infection when treated with amino-alcohol drugs, like, quinine. In severe falciparum malaria, the mortality rate is very high (20% to 30%) and even higher among non-immune patients.

Generally, the anti-malarial therapy by quinine could be a cause of BWF syndrome in severe falciparum malaria. The mechanism of intra-vascular hemolysis in G6PD-deficient patients as a response to primaquine-induced oxidative stress is well known [12]. Stephens [13] has summarized several reports associating quinine with BWF in patients with severe malaria in G6PD-deficient patients. Very little is known about the use of artemisinin (ART) or its derivatives [14] and their association with BWF, either alone or as part of artemisinin-based combination therapy (ACT) despite its high oxidative potential [15] [16] [17]. BWF has also been reported with other amino-alcohol drugs such as halofantrine [18] [19] [20], mefloquine [9] [10] and lumefantrine, a related aryl-amino-alcohol compound [16]. The BWF was not reported by chloroquine [3] or piperaquine derivatives in severe falciparum malaria despite its extensive use [21].

We present a rare case of black water fever developed in a Nigerian patient in a non-endemic malaria country, Kuwait, on second day of quinine treatment in severe falciparum malaria.

2. Case Summary

A 20-year-old Nigerian boy came to Kuwait on 16th September 2014 and he was complaining abdominal pain, nausea, vomiting and fever two days after his arrival. He has visited IDH casualty on 22nd September and his initial parameters registered like, high fever (40.8C), heart rate 125, blood pressure of 100/60 mmHg. The physical examination was unremarkable, including a normal neurologic examination, no hepatosplenomegaly, rash and neck rigidity. The initial laboratory tests revealed mild anemia (Hb, 126 g/L and HTC, 0.352 L/L, RBC, 4.12×10^{12}/L, WBC, 4.2×10^{9}/L and platelets 16×10^{9}/L) (Table 1). Most of his biological parameters, like liver enzymes, glucose, creatinine and total bilirubin were higher (Table 2). His G6PD was normal, 214.6 mU/10^{9} erythrocytes, (normal range 165 - 365 mU/10^{9} erythrocytes) and Pro-calcitonin was very high 125.4 (normal range 0 - 0.05) (Table 3). Giemsa stained thick and thin blood

Table 1. Hematological parameters during the treatment.

Parameters	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 30
RBC	4.12↓	3.8↓	3.11↓	3.07↓	3.15↓	3.12↓	3.26↓	3.2↓	4.05↓
WBC	3.5↓	6.71	6.1	7.9	10.6	12.6↑	15.8↑	15.2↑	6.5
HB	12.6↓	11.2↓	9.1↓	9.0↓	9.3↓	9.2↓	9.6↓	9.7↓	12.4↓
Platelets	16↓	27↓	19↓	19↓	28↓	96↓	148↓	224	195

Table 2. Biochemical laboratory values during treatment.

Parameters	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 30
Glucose	4.9	16.95↑	9.32↑	8.67↑	7.1↑	5.91	6.5↑	9.12↑	6.91↑	5.88
Na	135	134.9	134.8	134.6	132.4	134.4	131.7	130.6	133.3	138.5
K	3.45	5.29	3.73	4.05	4.01	3.97	3.82	4.2	4.56	3.83
Total Bilirubin	117.3↑	102.3↑	84.7↑	40.2↑	43.4↑	30.5↑	22.9↑	21↑	26.5↑	5.7
CO_2	22.2	27.8	24.3	20.6	22.7	23	22.2	23.2	25.6	25
Creatinine	139↑	122↑	93	74	63	66	70	76	80	95
Urea	7.8	5.7	5.6	3.5	3.8	3.7	3.30	2.4	2.5	3.5
ALT	28	26	22	19	26	-	106↑	102↑	99↑	28
AST	80↑	102↑	106↑	50↑	49↑	-	98↑	70↑	53↑	25
Alkaline Phosphatase	60	54	47	30	53	-	157↑	149↑	153↑	104
LDH	654↑	1114↑	1251↑	574↑	531↑	-	484↑	417↑	380↑	159↑
GGT	30	17	18	17	58↑	-	235↑	225↑	199↑	48

smears, and immunochromatographic (ICT) malaria test for the detection of histidine rich protein-2 (HRP2) antigen were used for the diagnosis of malaria. The ICT assay was performed as described by following the manufacturer's instructions. The Giemsa stained peripheral blood smears revealed the presence of all the sexual stages of *Plasmodium falciparum* (rings, trophozoites, and schizonts) (**Figure 1**). Rapid immunochromatographic test for histidine rich protein-2 (HRP2) (AccuBio Tech Co., Ltd Bejing, China) was also positive (**Figure 2**). The immunochromatographic test detects antigen in blood samples only if the parasite count is about 100 or more/μl of blood [22] [23]. The Giemsa stained thick and thin blood films examination confirmed the severe infection of *Plasmodium falciparum* with 41.0% parasitemia. The patient was admitted to the hospital and started intravenous Quinine (1200 mg loading dose in 5% glucose over 4 hours). The patient was feeling much better on next morning but became unconscious by evening and shifted to ICU. His all CBC parameters were higher and started passing dark/cola color urine. The 12 units of whole blood was exchanged on 24th September at morning time. He became fully conscious on 4th day and his anemia and thrombocytopenia was improved and the color of the urine also became normal. He was transferred to the general ward on 7th day and discharged from the hospital on 9th day without any symptoms of malaria.

Table 3. Key biochemical laboratory values during treatment.

Parameters	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 30
Procalcitonin	-	-	125.4↑ (0 - 0.5)	88.57↑	35.1↑	15.0↑	8.36↑	-	-
Lactate	-	-	2.19 (0.5 - 2.2)	-	-	-	-	-	-
G6PD act.	-	214.6 (165 - 365)	-	-	-	-	-	-	-
Parasitemia	41%	20.0%	1.2%	0.2%	0.1%	0.01%	Neg	Neg	Neg

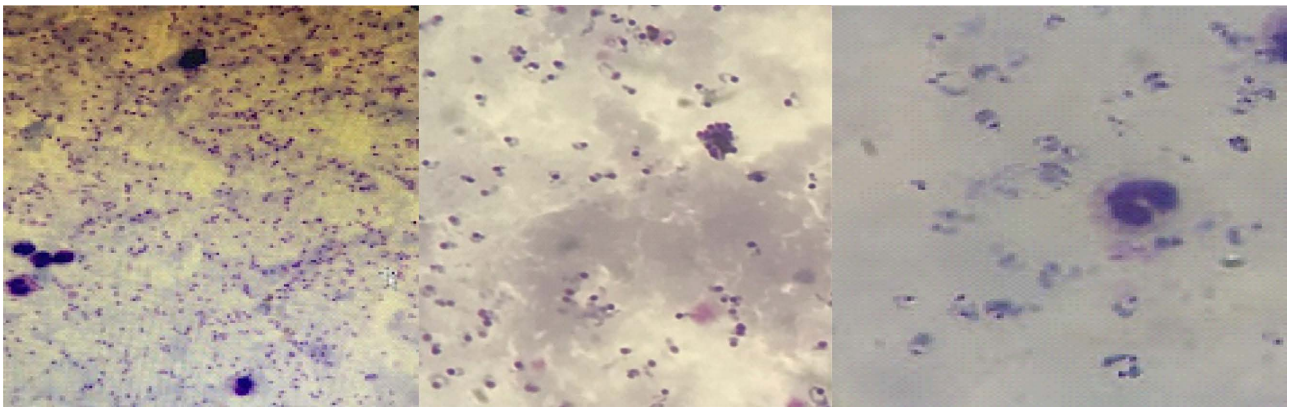

Figure 1. *Plasmodium falciparum* (trophozoites and schizonts) in thick blood film. Presence of schizonts shows the severity of the infection.

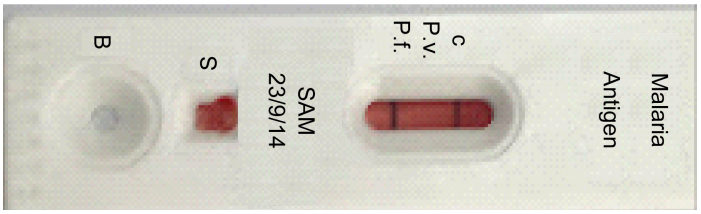

Figure 2. Pattern of rapid ICT malaria test. Presence of single positive line confirm *P. falciparum* infection only.

3. Discussion

Black water fever mostly occurs in *Plasmodium falciparum* infection and has a very high mortality rate. The symptoms developed in BWF are rapid pulse, high fever and chills, extreme prostration, a rapidly developing anemia, and the passage of urine that is dark black or cola in color. The dark/cola color of the urine is due to the presence of large amounts of hemoglobin released during the excessive destruction of the patient's erythrocytes by malarial parasites and causing severe anemia. The presence of blood pigments in the blood circulation usually produces jaundice early in the course of the disease.

Black water fever is mostly prevalent in Africa and Southeast Asia. The non-immune immigrants or individuals who are chronically exposed to malaria are the main vulnerable to infection and the victims of the complications. Black water fever seldom appears until a person has had at least four or more attacks of malaria and has been in an endemic area for six months. This patient came from the Nigeria with the history of several episodes of malaria. He was admitted in the hospital with fever, jaundice and body ache. The Giemsa stained thick and thin blood films were positive for *P. falciparum* and revealed all the stages of *P. falciparum* with 41% parasitemia. The treatment with quinine was started and after 12 hours the patient started passing dark/cola color urine and an increase of jaundice level. The treatment with quinine was suspended and coartem was started (four tablets as a single initial dose, 4 tablets again after 8 hours, and then 4 tablets twice-daily (morning and evening) for the following 2 days (total course of 24 tablets). The red blood cells and platelets were transfused and hemodialysis and plasmapheresis were also performed. The patient was discharged on 9th day when he became asymptomatic and his Giemsa stained blood films became negative. Treatment for black water fever includes antimalarial drugs, whole-blood transfusions, and complete bed rest, but even with these measures the mortality remains about 25 to 50 percent.

The black water fever is caused by the hemolysis of erythrocytes due to malaria and also with the metabolism of quinine by the cytochrome P450 3A4 enzyme responsible for increasing oxidative stress within erythrocytes, making these cells more vulnerable to hemolysis with falciparum malaria and G6PD deficiency. Oxidative stress is one of the major contributors to the manifestations of BWF in South Vietnam [24]. The prevalence of G6PD deficiency amongst malaria cases is high in this region and a few cases have G6PD mutants of diminished function in the presence of apparently normal G6PD levels [8]. The me-

tabolites of quinine may exert oxidative stress under particular conditions with acute hemolysis observed in G6PD deficient patients exposed to primaquine [24].

An alternate possibility is that anti-malarial drugs and the effects of immunity are the true cause of BWF. *P. falciparum* infections in human has severe effects on RBC function including changes in RBC size, deformability, endothelial adhesion and up regulation of particular outer membrane proteins including the ring-infected erythrocyte surface antigen (RESA) [25] [26]. In acute *P. falciparum* malaria the RESA is present on even non-parasitized RBCs, suggesting a circulating population of RBC "survivors" from which parasites have been removed by the spleen. This is thought to be why the fall in hematocrit seen in *falciparum* malaria is less than it would be predicted by the number of parasitized RBCs. In some circumstances it may be that once-infected erythrocytes (o-iE) become fatally inclined to non-immune oxidative hemolysis and this is done by anti-malarial drug therapy, in this case artemether with lumefantrine. This hypothesis gives very provocative information that BWF could be a deciding factor in a small number of patients who control an initial parasitemia at the expense of RBC predisposition to non-immune intravascular lysis that mimics or is caused by oxidative stress.

4. Conclusion

Quinine is managing both complicated and uncomplicated malaria and may precipitate black water fever in severe infection of *P. falciparum*. The black water fever is caused by the hemolysis of erythrocytes due to malaria and also with the metabolism of quinine by the cytochrome P450 3A4 enzyme responsible for increasing oxidative stress within erythrocytes, making these cells more vulnerable to hemolysis with falciparum malaria in G6PD deficient patients.

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Informed Consent Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest regarding the publication of this paper.

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